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(71) Applicant: AVON PRODUCTS, INC. [US/US]; 1251 Avenue of the Americas, New York, NY 11020-1196 (US).			
(72) Inventor: PTCHELINTSEV, Dmitri; 668 Juniper Way, Mahwah, NJ 07430 (US).			
(74) Agent: RUGGIERO, Charles, N., J.; Ohlandt, Greeley, Ruggiero & Perle, Suite 903, One Landmark Square, Stamford, CT 06901-2682 (US).			
(54) Title: ASCORBYL-PHOSPHORYL-CHOLESTEROL			
(57) Abstract			
<p>This disclosure relates to a derivative of L-ascorbic acid which is stable, easily incorporated into cosmetically acceptable vehicles and enzymatically bioreversible in the skin to free ascorbic acid and a safe alkanol component. The L-ascorbic acid derivative includes cholesterol. The L-ascorbic acid derivative is a compound selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol or homologs and salts thereof.</p>			

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ASCORBYL-PHOSPHORYL-CHOLESTEROL

Related Application

5 This application is a continuation-in-part of application Ser. No. 08/440,765, filed May 15, 1995, pending.

BACKGROUND OF THE INVENTION

I. Field of the Invention

10 The present invention relates to the synthesis and use of a novel derivative of L-ascorbic acid. This derivative of L-ascorbic acid includes cholesterol. The resultant product is stable, easily incorporated into cosmetically acceptable vehicles and enzymatically bioreversible.

15 II. Description of the Prior Art

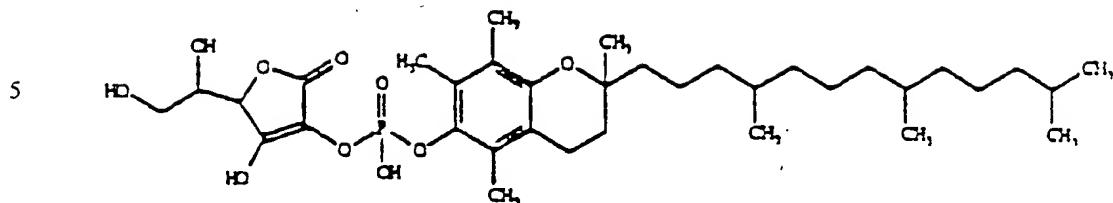
The use of L-ascorbic acid as an antioxidant in food preparations is known. For example, Steinhart, Pro- and Antioxidative Effect of Ascorbic Acid on L-Tryptophan in the Fe3+/Ascorbic Acid/O₂, J. Agric. Food Chem., Vol. 41, pages 2275-2277 (1993) describes the use 20 of L-ascorbic acid as an antioxidant that functions in food to remove free radicals and undergoing rapid oxidation.

Similarly, free L-ascorbic acid in topical preparations demonstrates poor stability and tends to break down due to partially oxidative and non-oxidative degradation. The degraded ascorbic acid 25 loses activity and the resultant product loses aesthetic appeal since it exhibits a cosmetically undesired brown color.

While cholesterol is considered unhealthy especially when ingested, the benefits of cholesterol, necessitated with L-ascorbic acid, for skin barrier repair are known. For example, Menon, Structural Basis for the Barrier Abnormality Following Inhabitations of HMG CoA Reductase in Murine Epidermis, J. Invest. Dermatol., Vol. 98, pages 209-219 (1992), describes deficiencies in the skin barrier repair mechanism when cholesterol synthesis is inhibited by regulation of HMG CoA reductase.

Presently, mechanical mixing of L-ascorbic acid and cholesterol results in an unstable product due to the instability of L-ascorbic acid. For example, U.S. Patent No. 4,939,128 to Kato is directed to the use of phosphoric acid esters of ascorbic acid for the treatment of diseases, not for cosmetics, topical dermatological or skin uses, and teaches that certain phosphoric acid esters of ascorbic acid display improved oxygen scavenging properties. One of the phosphoric acid esters in the patent is substituted with a cholestanyl group. The conspicuous absence of cholesterol and the specific mention of a cholesteryl group recognizes that conjugates of L-ascorbic acid and cholesterol were then not practical or desired.

Attempts have been made to conjugate ascorbic acid with a glycyrrhetic group as described in European Application No. 92104149.7; and with a tocopheryl group as indicated by U.S. Patent No. 3,151,127. U.S. Patent Nos. 4,564,686 and 5,306,713 disclose tocopheryl ascorbyl phosphate as an anti-oxidant having the following structure:



Also, Sakamoto, Measurement Method of Efficacy of
Antidandruff Cosmetics and Development of the New Active
Commercial Product, IFSCC, Yokohama, Vol. B206, pages 823-864
(1993) describes the use of tocopheryl coupled to L-ascorbic acid. The
coupled tocopheryl is an antioxidant preservative for the ascorbyl group,
but the use of the ascorbyl-tocopheryl as a skin therapeutic is
15 questionable since, unlike cholesterol, tocopheryl is not a natural
substrate for the skin.

Heretofore, there has been needed a stable product having
cholesterol coupled to L-ascorbic acid, which product retained full
functional activity even after decoupling by naturally occurring acidic
20 phosphatases in the skin. This product would provide the beneficial
properties of L-ascorbic acid, including increased collagen production
and skin-lightening, combined with the benefits of released cholesterol,
namely improved elasticity, resistance, tone and moisture retention of
the skin. Accordingly, there has been needed a method for covalently
25 and bioreversibly effecting the coupling of cholesterol to L-ascorbic acid.

SUMMARY OF THE INVENTION

It is an object of the present invention such a stable composition that is a novel derivative of L-ascorbic acid that includes cholesterol.

It is another object of the present invention to provide to provide such a stable composition of cholesterol coupled to L-ascorbic acid for 5 use in cosmetic products.

It is still another object of the present invention is to provide such a stable composition having multiple skin care benefits.

It is a further object of the present invention is to provide such a stable composition that is easily carried in cosmetic vehicles, 10 enzymatically bioreversible, and demonstrates extended shelf-life.

It is yet a further object of the present invention is to provide a method for covalently and bioreversibly coupling cholesterol to L-ascorbic acid for stabilization of the resulting molecule.

To accomplish the forgoing objects and advantages, the present 15 invention, in brief summary, is a derivative of L-ascorbic acid that includes cholesterol. Such derivatives are, for example, 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol or homologs and their salts thereof.

These and other objects of the present invention will become evident from the invention described below.

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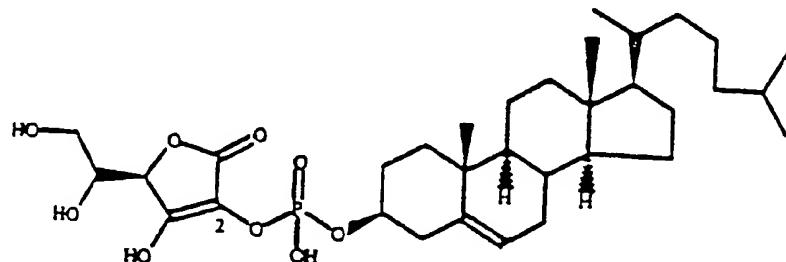
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention includes a novel derivative of L-ascorbic acid. The derivative is formed by a coupling of L-ascorbic acid and cholesterol. The novel derivative, that can be easily included in a 25 suitable topical vehicle, is selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol, 3'-(L-ascorbyl-3-o-phosphoryl)-cholesterol or homologs and their salts thereof. The exemplary

compounds include functional or structural homologs of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol (Formula I) such as 3'-(L-ascorbyl-3-o-phosphoryl)-cholesterol (Formula II). Both formulas are illustrated below.

Formula I

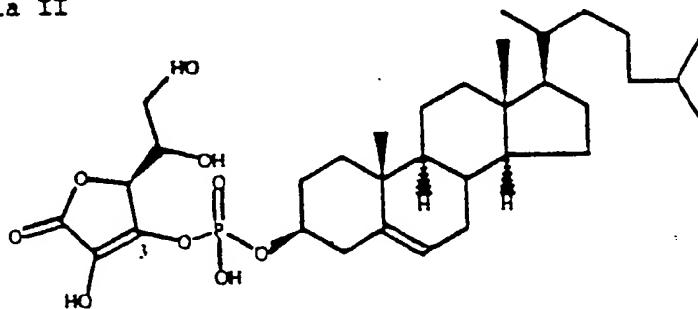
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Formula II

15



The L-ascorbic acid is covalently bounded to the cholesterol by phosphoryl or phosphates so that the L-ascorbic acid derivative set forth above is also called ascorbyl-phosphoryl-cholesterol.

20

In the ascorbyl-phosphoryl-cholesterol compounds of the present invention, the conjugated ascorbic acid becomes resistant to degradation. The cholestryl group serves as a carrier moiety and facilitates delivery of polar ascorbic acid through the non-polar outermost protective layer of skin (i.e., the stratum corneum) and increases the bioavailability of the ascorbic acid in the topical application.

Natural enzymes, such as phosphatases present in the skin, gradually cleave the phosphoryl or phosphate linkage between cholesterol and ascorbic acid, resulting in sustained release of free L-ascorbic acid and cholesterol into the stratum corneum. The released 5 cholesterol is a natural substrate for skin and supplements that otherwise produced by the body. Topically applied cholesterol improves elasticity, tone and resistance to drying.

The basic topical formula may comprise from about .0001 to about 100, with all ranges set forth in weight percent, of the L-ascorbic acid derivative. In a preferred embodiment, about .05 to about 50 weight percent of the L-ascorbic acid derivative is in a cosmetically acceptable vehicle. In a more preferred embodiment, about .10 to about 20 weight percent of the L-ascorbic acid derivative is combined with a cosmetically acceptable vehicle, and in an even more preferred 15 embodiment about 1.0 to about 10 weight percent. Salts of the L-ascorbic acid derivative, namely ammonium, calcium, lithium, potassium or sodium can be incorporated with the L-ascorbic derivative into a cosmetically acceptable vehicle. A salt with an organic amine, such as ethanolamine, may also be used in combination with the L-ascorbic acid 20 derivative.

Suitable vehicles include conventional lotions, creams or gels. A "physiologically acceptable vehicle" or a "suitable vehicle" means drugs, cosmetics, medicaments or inert ingredients that are suitable for use in direct contact with human tissues without undue toxicity.

25 A first or more basic lotion comprises about 0.10 to about 20.0 weight percent of the L-ascorbic acid derivative, and the remainder is or includes water. Most preferably, the L-ascorbic acid derivative is 3'-(L-

5 ascorbyl-2-o-phosphoryl)-cholesterol (Formula I) or 3'-(L-ascorbyl-3-o-phosphoryl)-cholesterol (Formula II) and, preferably, the L-ascorbic acid derivative is homologs and/or salts thereof. A second lotion has about .10 to about 20.0 weight percent L-ascorbic acid derivative, about .001 to about 1.5 weight percent thickener or thickening agent, and the remainder is or includes water. The second lotion may also include up to about 1.0 weight percent fragrance.

10 Examples of thickening agents suitable for use with the L-ascorbic acid derivative include xanthene gum, xanthene gum brine tolerant, hydroxypropyl cellulose, hydroxyethyl cellulose, carbopol and gum acacia, Sepigel 305 (available from Seppic Co., France), vee-gum or magnesium aluminum silicate or combination thereof. The thickening agent is preferably xanthene gum or hydroxyethyl cellulose or a combination thereof.

15 A third lotion has, besides about 0.10 to about 20.0 weight percent L-ascorbic acid derivative, about 0.50 to about 1.40 weight percent of a thickening agent, about 0.50 to about 6.0 weight percent of an emollient, about 4.8 to about 14.5 weight percent of an emulsifier, and the remainder is or includes water. It may also include about 0.35 to about 0.45 weight percent of a preservative.

20 In the third lotion, the thickening agent is preferably about 0.25 to about 0.70 weight percent of xanthene gum, and about 0.25 to about 0.70 weight percent of hydroxyethyl cellulose. The emollient, which can be a humectant, preferably is glycerin. The emulsifier is preferably a combination of emulsifiers, namely about 2.0 to about 8.0 weight percent of propylene glycol decapitate, about 1.8 to about 4.0 weight percent of Peg 40 Stearate, and about 1.0 to about 2.5 weight percent

of Steareth-2. The preservative is preferably about 0.15 to about 0.20 weight percent of disodium EDTA or EDTA salt, and about 0.20 to about 0.25 weight percent of methylparaben.

A second cosmetic vehicle, a cream, comprises about 0.10 to 5 about 20.0 weight percent of the L-ascorbic acid derivative, about 0.1 to about 1.20 weight percent of a thickening agent; about 0.1 to about 15 weight percent of an emulsifier, and the remainder is or includes water. It may also include up to about 1 weight percent of fragrance.

A second, less preferable, cream has about 0.5 to about 4.0 10 weight percent of an emollient, preferably glycerin; about 2.0 to about 6.0 weight percent of an emollient/humectant, preferably propylene glycol; emulsifiers, preferably about 1.8 to about 3.0 weight percent Steareth-20, about 0.8 to about 2.0 weight percent Steareth-2, about 1.0 to about 2.5 weight percent cetyl alcohol, and about 0.9 to about 3.5 15 weight percent glycerol mono-stearate; thickening agents, such as about 0.25 to about 0.6 weight percent xanthene gum and about 0.25 to about 0.6 weight percent hydroxyethyl cellulose; and a preservative, preferably about 0.15 to about 0.2 weight percent disodium EDTA or EDTA salt.

While such lotions or creams can be made by conventional 20 homogenization methods, such lotions and creams can also be made by a process of microfluidization that involves co-mixing the aqueous phase and the oil phase of such creams and lotions in a high-pressure homogenizer that reduces the emulsion particle size dramatically to about 1/400th the size of those in creams and lotions prepared without 25 applying high pressure. Microfluidization permits the preparation of elegant stable creams and lotions containing effective amounts of the L-

ascorbic acid derivative without the use of traditional emulsifiers and surfactants.

With respect to the L-ascorbic acid derivative in a gel vehicle, a first or preferred gel has about 0.10 to about 20 weight percent L-
5 ascorbic acid derivative, about 0.30 to about 2.0 weight percent thickening agent, and the remainder includes water. A second or less preferred gel has about 0.10 to about 20.0 weight percent L-ascorbic acid derivative; about 2.0 to about 6.0 weight percent of an emollient/humectant, preferably propylene glycol; about 0.4 to about 1.5
10 weight percent of a thickening agent, preferably hydroxyethyl cellulose; and a preservative, preferably about 0.15 to about 0.20 weight percent disodium EDTA or EDTA salt and about 0.20 to about 0.25 weight percent methylparaben.

The pH of the lotion, cream or gel formulas can be adjusted to
15 physiologically acceptable levels with sufficient amounts (preferably about 3.0 to about 7.5 weight percent) of ammonium hydroxide, calcium hydroxide, lithium hydroxide, potassium hydroxide, sodium hydroxide, ethanolamine, diethanolamine or urea.

As stated above, an emollient used in the above lotion, cream
20 and gel formulas is glycerin and an emollient/humectant is propylene glycol. Besides such emollients, the L-ascorbic acid derivative or the lotion, cream or gel formulas can also be combined with most other conventional emollients, such as mineral oil, petrolatum paraffin, ceresin, ozokerite, microcrystalline wax, perhydrosqualene, dimethyl
25 polysiloxanes, methylphenyl polysiloxanes, silicone-glycol copolymers, triglyceride esters, acetylated monoglycerides, ethoxylated glycerides, alkyl esters of fatty acids, fatty acids and alcohols, lanolin and lanolin

derivatives, polyhydric alcohol esters, sterols, beeswax derivatives, polyhydric alcohols and polyethers, and amides of fatty acids. Other suitable emollients can be found in Sagarin, Cosmetics, Science and Technology, 2nd Ed., vol. 1, pp. 32-43 (1972), the contents of which are 5 incorporated by reference herein.

In the above formulas, the emulsifiers can be cationic, anionic, non-ionic, amphoteric, or a combination thereof. A non-ionic emulsifier is preferred. As set forth above, the non-ionic emulsifiers propylene glycol decapitate, PEG 40 Stearate, Steareth-20, Steareth-2 and cetyl 10 alcohol are used in various formulas. Examples of other non-ionic emulsifiers are commercially available sorbitans, alkoxyolated fatty alcohols and alkyl polyglycosides. Anionic emulsifiers may include soaps, alkyl sulfates, monoalkyl and dialkyl phosphates, alkyl sulphonates and acyl isethionates. Other suitable emulsifiers can be 15 found in McCutcheon, Detergents and Emulsifiers, North American Edition, pp. 317-324 (1986), the contents of which are incorporated herein by reference.

Other suitable preservatives, besides Distoma EDTA and methylparaben set forth above, include alkanols, especially ethanol and 20 benzyl alcohol, parabens, sorbates, urea derivatives and isothiazolinones.

Suitable humectants include urea, PCA, amino acids, certain polyols and other compounds with hygroscopic properties.

The present invention includes topically applying an effective amount in a physiologically acceptable vehicle to a skin area, normally 25 once or twice daily. The effective amount and the frequency of application will vary depending on the particular skin, the age and

physical condition of the person, and like factors within the knowledge and expertise of those skilled in the art.

The L-ascorbic acid derivative in an amount about .05 to about 10 weight percent, and more preferably about .05 to about 5 weight percent, can be in topical compositions alongside keratolytic agents and skin lightening agents. The keratolytic agents may include salicylic acid and benzoyl peroxide. The skin lightening agents may include kojic acid, benzoquinone, licorice derivatives, magnesium ascorbyl phosphate, glycerhetinic acid and its derivatives.

10 The L-ascorbic acid derivative in an amount about 0.001 to about 25 weight percent can also be used with organic and inorganic sunscreens, such cinnamic acid derivatives (menthyl, octyl, 2-ethylhexyl, benzyl, alphaphenyl cinnamonnitrile, and butyl cinnamoyl pyruvate), titanium dioxide, zinc oxide, benzylidene camphor, anthranilates, and 15 naphtholsulphonates. The cinnamic acid derivatives are preferred.

15 About .001 to about 10 weight percent, and more preferably about .001 to 5 weight percent of the L-ascorbic acid derivative can be co-formulated with (a) retinoids, (b) hormonal compounds, (c) alpha-hydroxyacids or polyhydroxy alpha-hydroxy acids, or (d) alpha-keto acids.

20 The retinoids include, for example, retinol, retinoic acid, retinyl palmitate, retinyl propionate, retinyl acetate, isotretinoin and synthetic retinoid mimics. The hormonal compounds include, for example, estriol, estradiol, estrone or conjugated estrogens. The alpha-hydroxyacids or 25 polyhydroxy alpha-hydroxy acids include, for example, glycolic acid, lactic acid, tartaric acid, gulonic acid and other carboxylic acids and their monomeric, polymeric, cyclic or acyclic derivatives. The alpha-keto

acids include, for example, pyruvic acid, 2-oxopropanoic acid, 2-oxobutanoic acid, 2-oxopentanoic acid and the like.

The L-ascorbic acid derivative can be used for additional benefits in topical formulations that include the following ingredients:

- 5 vitamins, enzyme co-actors such as vitamin B6, vitamin B12, vitamin D3, 1,25-dihydroxy vitamin D3, vitamin B1, riboflavin, vitamin K, vitamin E, tocotrienols and their derivatives, nicotinic acid and its esters, pantothenic acid and its esters, panthenol, folic acid and its derivatives, choline, carnitine and substances without formal vitamin status or
- 10 "pseudo-vitamins" such as vitamin F or cis, cis-linoleic acid, vitamin M or pteroylglutamic acid, vitamins B10 and B11, sesame seed factor, termitin, penicin, insectine, hypomycin and mycoine, vitamin L or anthranilic acid, vitamin L2 or adenylthiomethyl-pentose, myoinositol or cis-1,2,3,5-trans-4-6-cyclohexanehexol and its esters, especially phytic acid, laetnile or 1-mandelo-nitrile-beta-glucuronic acid, amygdalin, vitamin B15 or pangamic acid, vitamin B13 or orotic acid, vitamin H3 or procaine hydrochloride, vitamin U or methyl-sulfonium salts of methionine and pyrroloquinoline quinone, or effective amounts of antifungal agents such as clotrimazole, ketoconazole, miconazole,
- 15 naftifine, tolnaftate, amphotericin B, nystatin, 5-fluorocytosine, griseofulvin, haloprogin, of which tolnaftate, haloprogin and miconazole are most preferred. In formulas that include one or both of the preferred, the L-ascorbic acid derivative is present in an amount from about .001 to about 10 and, more preferably, about .001 to about 5
- 20 weight percent.
- 25

About .001 to about 20 weight percent of the L-ascorbic acid derivative can be used with one or more of:

(1) self-tanning agents, such as dihydroxyacetone and lawsone, with the former one being most preferred;

(2) anti-mycobacterial agents, such as erythromycin, tetracyclin and related compounds, especially doxycyclin and methacyclin,

5 cephalosporine, penicillins, macrolides, peptide compounds selected from the group consisting of novobiocin, vancomycin, oleandomycin, paromomycin, leucomycine, amphotomycin with macrolide molecules preferred over the polypeptide compounds, quinolone derivatives, and other compounds which interfere with bacterial cell wall synthesis,

10 membrane function, RNA metabolism, puline, pyrimidine and protein synthesis, respiration or phosphorylation;

(3) topical analgesics, such as lidocaine, benzocaine, butamben, butacaine, tetracaine, clove oil, eugenol, with lidocaine and benzocaine being most preferred;

15 (4) lipidic compounds essential for the skin's barrier function such as ceramides, essential fatty acids and their esters, especially glycerides, ω -hydroxy fatty acids and their esters derived with alkanols through carboxylic hydroxyl or with other fatty acids at the omega-hydroxyl, the latter type being most preferred, with phospholipids. The

20 lipidic compounds can be added to a topical composition either as singular molecular entities or as a complex mixture of lipids derived from either synthetic, animal or plant sources;

(5) antiallergenic agents and H1 and/or H2 antihistamines, such as diphenylhydramine, clemizole, antazoline, thenaldine,

25 phenyltoloxamine citrate, tricyclic antiallergenics, such as ketotifene, dithiadene and 3-thienylsulfide of thiadene, H2-receptor blockers,

especially burimamide, metiamide and cimetidien, cromolic acid and its salts;

(6) the L-ascorbic acid derivative can be used with topical anti-inflammatory agents that can reduce inflammation. These agents are at 5 a concentration from about 0.001% to about 10%, preferably, about 0.5 to about 1%, with the concentration of the anti-inflammatory adjusted up or down depending upon the potency of the utilized agents. Examples of steroidal anti-inflammatories that can be used with the L-ascorbic acid derivative include hydrocortisone, hydroxytriamcilon, alpha-methyl 10 dexamethasone, dexamethasone phosphate, beclamethasone dipropionate, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, prednisolone, prednisone, and mixtures thereof, with the most preferred being prednisolone and hydrocortisone;

(7) non-steroidal anti-inflammatories can also be employed, 15 such as described in Rainsford, Antiinflammatory and Anti-Rheumatic Drugs, Vols. I-III, CRC Press, Boca Raton, Florida (1985). Specific examples of suitable non-steroidal anti-inflammatories include oxicams (e.g. piroxicam, isoxicam), fenamic acid derivatives, meclofenamic acid derivatives (e.g. sodium meclofenamate), flufenamic acid derivatives, 20 mefenamic acid derivatives, propionic acid esters, such as ibuprofen, naproxen, benoxaprofen, flubiprofen, ketoprofen, suprofen, with ibuprofen being most preferred; pyrazolidinediones, with phenylbutazone being most preferred; the acetic acid derivatives, such as diclofenec, fenclofenac, indomethacin, sulindac, with indomethacin 25 being most preferred; salicylic acid derivatives, such as aspirin, disalacid, benorylate, with aspirin and disalacid being most preferred.

The compositions of the present invention may also include safe anti-inflammatory products of natural origin shown to possess anti-inflammatory activity such as aloe vera extracts, extracts from genus Rubis (Rubia Cordifolio), extracts from genus Commiphom (Commiphora Mukul), Willow bark, matricaria flowers, arnica flower, comfrey root, fenugreek seed and the like known to those skilled in the art.

About .001 to about 20 weight percent of the L-ascorbic acid derivative can be used in formulas that contain anti-oxidants with phenolic hydroxy functions, such as gallic acid derivatives (e.g. propyl gallate), bio-flavonoids (e.g. quercetin, rutin, daidzein, genistein), ferrulic acid derivatives (e.g. ethyl ferrulate, sodium ferrulate), 6-hydroxy-2,5,7,7-tetra-methylchroman-2-carboxylic acid. The compositions may also contain effective concentrations of water soluble anti-oxidants such as, for example, uric acid, reductic acid, tannic acid, rosmarinic acid and catechins. Also the L-ascorbic acid derivative can be co-formulated with nitric oxide synthase inhibitors to reduce skin redness, vasodilation and inflammatory reactions, especially in response to electromagnetic and ionizing radiation or to the action of chemically or biochemically aggressive compounds. The nitric oxide synthase inhibitors can be added at concentrations from about 0.05% to about 10%, most preferably from about 1% to about 3%. The nitric oxide synthase inhibitors are selected from the group consisting of guanidine derivatives, especially monoaminoguanidine and methylguanidine, L-arginine derivatives, especially N^G-nitro-L-arginine and its esters, N^G-monomethyl-L-arginine, 2-iminopiperidines and other 2-iminoazaheterocycles.

Other possible anti-oxidants that the derivative may contain are those that have one or more thiol functions (-SH) in either reduced or non-reduced form such as glutathione, lipoic acid, thioglycolic acid and other sulfhydryl compounds. The levels of sulfhydryl anti-oxidants 5 should not exceed 0.5% for cosmetic uses of the composition, but may be higher for pharmaceutical uses as dictated by the considerations of efficacy. The composition may also include inorganic anti-oxidants, such as sulfites, bisulfites, metabisulfites or other inorganic salts and acids containing sulfur in oxidation state +4. The preferred level of 10 inorganic sulfur-containing anti-oxidants is about 0.01 to about 0.5 with the most preferred level about 0.1% to about 0.4 by weight percent.

The L-ascorbic acid derivative may be used with about 0.025% to about 5%, preferably about 0.5 to about 3 weight percent, and most preferably about 0.5 to about 1 weight percent, of compounds known to 15 be electron spin-traps, such as nitrones, N-tert-butylnitron and α -[4-pyridyl 1-oxide]-N-tertbutyl nitron or other compounds known to form free radicals with half-life time of more than 1 min.

About .001 to about 50 weight percent of the L-ascorbic acid derivative can also be used in compositions that contain insect 20 repellents such as aliphatic, cyclic or aromatic amides, citronella oil, terpineol, cineole, neem oil and terephthalic acid and its esters. Other suitable insect repellents can be found in Technical Bulletin No. 1549 from the U.S. Department of Agriculture or in their Agricultural Handbook Nos. 69, 340 and 461.

25 The about .001 to about 50 weight percent L-ascorbic acid derivative is also suitable for topical compositions that contain skin cooling compounds such as, for example, menthol, menthyl glycerol,

asymmetrical carbonates, thiocarbonates and urethanes, N-substituted carboxamides, ureas or phosphine oxides such as described in J. Cosmet. Cham., vol. 29, p. 185 (1978), methyl lactate and menthone glycerine acetal.

5 The L-ascorbic acid derivative can be used with other cosmetic and pharmaceutical actives and exponents, such as, for example, antifungals, antiallergenic agents, depigmenting agents, antiinflammatory agents, anesthetics, surfactants, moisturizers, exfoliants, stabilizers, antiseptics, lubricants, chelating agents and skin 10 penetration enhancers. When used with these ingredients, the L- ascorbic acid derivative may provide additional dermatological and/or cosmetic benefits.

15 The L-ascorbic acid derivative can also be formulated in the form of micro-emulsions. The micro-emulsion system would typically contain an effective amount of the L-ascorbic acid derivative, up to 18% of a hydrocarbon, up to 40% of an oil, up to 25% of a fatty alcohol, up to 30% of a non-ionic surfactant, and up to 30% of water.

20 The L-ascorbic acid derivative is suitable and convenient for use in topical products formulated in the form of oil-in-water or water-in-oil emulsions, ointments, sticks, sprays, tapes, patches, as multiphase emulsion compositions, such as water-in-oil-in-water type as disclosed in U.S. Patent No. 4,254,105, incorporated herein by reference. The L- ascorbic acid derivative can also be formulated as triple emulsions of 25 the oil-in-water-silicone fluid type as disclosed in U.S. Patent No. 4,960,764 incorporated herein by reference.

The L-ascorbic acid derivative can also be made as a liposomal formulation, for example, according to the methods described in Mezei,

J. Pharmaceut. Pharmacol., vol. 34, pp. 473-474 (1982) or modification thereof. In such compositions, droplets of the L-ascorbic acid derivative can be entrapped inside the liposomal vesicles and then incorporated into the final formula with the shell of the liposome being a phospholipid 5 but which can be replaced with other suitable lipids (e.g., skin lipids). The liposomes can then be added to any carrier system described above according, for example, to the preparation modes, uses and compositions of topical liposomes as described in Mezei, Topics in Pharmaceutical Sciences, Breimer et al. Eds., pp. 345-358, Elsevier 10 Science Publishers BV, New York (1985), incorporated herein by reference, or according to the reverse-phase evaporation method described in Szoka et al., Proc. Nat. Acad. Sciences, vol. 75, pp. 4194-4198 (1978), and also in Diploses et al., J. Soc. Cosmetic Chemists, vol. 43, pp. 93-100 (1992), all incorporated herein by reference.

15 The L-ascorbic acid derivative can also be entrapped in polymeric vesicles with a shell consisting of a suitable polymeric material, such as gelatin, cross-linked gelatin, polyamide, polyacrylates and the like. These vehicles can then be incorporated into any composition set forth herein.

20 The general activity and mildness to skin can also be enhanced by neutralization to pH 3.5 to 8.0, most preferably from pH 3.7 to 5.6, with one or more amphoteric and pseudoamphoteric compounds selected from a group including, but not limited to, glycine, alanine, valine, serine, threonine, methionine, leucine, asparagine, histidine, 25 glutamic acid, glutamine, lysine, cystine, cysteine, tryptophan, serine, phenylalanine, citrulline, creatine, proline, 3- or 4-hydroxyproline, 5-hydroxylysine, ornithine and its derivatives, 3-aminopropanoic acid and

other aminocarboxylic acids, canavanine, canaline, homoarginine, taurine, aminoaldonic acids and aminosugars, aminouronic acid, aminoaldaric acid, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, desulfated heparin, neuraminic or sialic acid, methionine 5 sulfone, glycylglycine, chondroitin, D,L-sphingosine, sphingomyelin, ophidine, glucagon, homocarnosine, phosphatidyl serine, cocoamphoglycine, phosphatidyl ethanolamine, cysteinesulfinic acid, glutathione, amphoteric inorganic oxides, polyamidoamines, polyamidoamines-based dendrimers, sodium hydroxymethylglycinate 10 and polyethylene amine.

When about .001 to about 20 of L-ascorbic acid derivative is used with certain chelating agents, the utility and mildness of the composition can also be enhanced. The chelating agents should be from about 0.01 to about 25, more preferably from about 0.5 to about 15 10, and most preferably from about 1 to about 5 weight percent.

Suitable examples of chelating agents include those that have a high affinity for zinc, calcium, magnesium, iron and/or copper ions, such as ethylene-diamine-tetra-acetic acid (ethylenedioxy)-diethylene-dinitriolo-tetra-acetic acid, salicylaldoxime, quinolinol, diaminocyclohexane-tetra- 20 acetic acid, diethylene-triaminopenta-acetic acid, dimethylglyoxime, benzoin oxime, triethylenetetramine, desferrioxamine or mixtures thereof.

The L-ascorbic acid derivative has been unexpectedly and surprisingly found to be useful as active agent in topical preparations for 25 treating signs of dermatological aging, both photoaging and intrinsic aging, including skin wrinkles such as fine wrinkling in the eye areas or "crows feet," or fine wrinkles around the mouth area, irregular

pigmentation, sallowness, loss of skin resilience and elasticity. The present compound is also useful for treating disorders associated with the nails, cuticles and hair such as ingrown hair, folliculitis and Pseudofolliculitis barbae. It has been discovered that the present 5 compounds soften hair and promotes the elimination of hair ingrowths, and are particularly useful for shaving.

The L-ascorbic acid derivative also enhances protection against UV provided by known sunscreen formulations.

The present invention also relates to a method for coupling a 10 molecule of L-ascorbic acid to a molecule of cholesterol. The coupling preferably occurs through a bioreversible phosphate linkage at position 2 or 3 on the ascorbyl group and position 3' on the cholesteryl moiety. Resulting compositions are also contemplated by this invention.

Formula I was formed by preparing the conjugated 3'-(L- 15 ascorbyl-2-o-phosphoryl)-cholesterol by dissolving cholesterol at -10 degrees C in dry diethyl ether (dried with 4A molecular sieves) containing 1.0 equivalent of triethylamine as a base. Phosphorous oxichloride (1.0 equivalent) was added to provide cholesteryl phosphorodichloridate.

20 The melting point of the cholesteryl phosphorodichloridate was measured as 121-122 degrees C and infrared (KBr pellet) analysis showed P=O absorption at 1298 wavelengths and P-O-C absorption at 1019 wavelengths, with no hydroxyl absorption. Cholesteryl phosphorodichloridate was subsequently reacted for 3 hours at room 25 temperature with 5,6-isopropylidene-L-ascorbic acid in tetrahydrofuran containing 1.0 equivalent of triethylamine. This reaction yielded a mixture of cholesteryl 5,6 isopropylidene-2-phosphorochloridate L-

ascorbic acid and its isomer cholestryl 5,6-isopropylidene-3-phosphorochloridate L-ascorbic acid.

The isomeric moisture was hydrolyzed in an aqueous solution of THF and stirred for several hours at room temperature with Amberlyst-5, a strongly acidic sulfonic acid ion exchange resin. THF and water were then removed. The final product, 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol, was extracted with ethyl acetate and neutralized with an KOH equivalent. The resulting solution was lyophilized to obtain the monopotassium salt form.

10 This novel method permits covalent and bioreversible coupling of cholesterol with L-ascorbic acid resulting in the stabilization of ascorbic acid, and increased bioavailability for ascorbic acid and cholesterol.

15 The compounds of the present invention are generally synthesized by reacting cholesterol with a halogenophosphorelating agent, (b) coupling the resulting product with 5,6-hydroxyl protected L-ascorbic acid, (c) hydrolyzing the product with water, (d) stripping the protective group with an acidic resin and (e) purifying the product with lyophilization and recrystallization. The derivative is stable in solution, 20 exhibits anti-oxidant activity and stimulates production of collagen in fibroblasts.

EXAMPLE 1

Preparation of Phosphodiester

Acid and its Mono Potassium Salt

Cholesteryl phosphodichloride was synthesized using the following procedure. A 250 ml two neck 19/22 ST round bottom flask was selected for the reaction. It included a serum cap (with nitrogen inlet needle), a stirring bar and a 19/22 to 24/40 ST 125 ml dropping funnel equipped with a side arm. This apparatus was flame dried and cooled under a nitrogen sweep. The dropping funnel was charged with 4.64 grams (12 mmole) of Sigma 99+% cholesterol, 75 ml of ether (dried over activated 4A molecular sieves) and 1.214 grams (12 mole, 1.672 ml) of dry (over KOH) triethylamine.

10 The flask was charged with 28 ml of dry ether and 1.84 grams (12 mole, 1.118 ml) of phosphorous oxychloride and cooled in an ice/methanol (-10 degrees C) bath. Ether containing the cholesterol-triethylamine was added dropwise at a brisk rate over a period of 20 to 30 minutes. The solution was warmed to room temperature and stirred 15 for 2.5 hours.

Precipitated solids were filtered off on a Buchner funnel and washed three times in water with thorough stirring. Air was introduced through the Buchner funnel until all of the ether in the filtrate evaporated. Solid precipitate was then removed by filtration through a 20 second Buchner funnel and cholesteryl phosphodichloride was dried in a vacuum desiccator over phosphorous pentoxide. This experiment yielded 3.90 grams (65%) of first crop solid, mp 121-122 degrees C and 1.74 grams (29%) of second crop material, mp 117-118 degrees C. IR analysis (KBr pellet) showed (C-H) absorption at 2947 wavelengths, 25 (=C-H) absorption at 2878 wavelengths, (C=C) absorption at 1466 wavelengths, (P=O) absorption at 1298 wavelengths and (P-O-C) absorption at 1019 wavelengths.

Ascorbic cholesteryl phosphodiester chloride was synthesized following the procedure as outlined below.

A 50 ml three neck, 19/22 ST round bottom flask fitted with a stirring bar, serum cap, nitrogen inlet needle and 50 ml dropping funnel 5 was selected for this experiment. This apparatus was flame dried and cooled under a nitrogen sweep. The dropping funnel was charged with 503 mg (1 mmole of cholesteryl phosphorodichloride (mp 122 degrees C) and 15 ml of dry THF, and the mixture was cooled in an ice/methanol bath (-10 degrees C). To the cooled mixture was added 216 mg (1 10 mmole) of Sigma 5,6-isopropylidene-L-ascorbic acid, 15 ml of dry THF and 0.14 ml (101mg, 1 mmole) of dry (KOH) triethylamine. After addition, the mixture was warmed to room temperature and stirred for 3 hours.

A TLC (25% methanol/toluene) analysis indicated the reaction 15 was complete. It also suggested that the product was a mixture of 2-O and 3-O regioisomers. The precipitated triethylamine hydrochloride was removed by filtration through fluted paper. THF was removed by rotary evaporation to provide 0.66 grams (97%) of crude crystalline ascorbic cholesteryl phosphodiester chloride.

20 Ascorbic cholesteryl phosphodiester acid was prepared utilizing the following procedure. Crude ascorbic cholesteryl phosphodiester chloridate (6.76 grams, 9.9 mmole) in 60 ml of THF was combined with 30 ml of water and 20 grams of wet Amberlyst-15 that had been rinsed in water three times. The resulting mixture was stirred vigorously at 25 room temperature for 55 hours. Amberlyst-15 was removed by filtration through fluted paper and was rinsed once with 20 ml of 1:1 THF/water.

Most of the THF was removed in a stream of nitrogen to provide 53 ml of a thick cloudy aqueous suspension.

Fifty three (53) ml of THF was added to the suspension to yield 106 ml of 1:1 THF/water solution of crude phosphodiester acid that was 5 nearly clear. Phosphodiester acid was purified by adding the 1:1 THF/water solution to a column of C-18 reverse phase silica gel (472 grams) and eluting with 1:1 THF/water. THF was removed in a stream of nitrogen to give 215 ml of purified phosphodiester acid in aqueous suspension. The projected total yield was 1.74 grams (28%), and the 10 actual isolated yield was 1.84 grams (30%). Reverse phase HPLC analysis indicated 90% purity.

Ascorbic cholesteryl phosphodiester diacid mono potassium salt was made by first treating a 1% aqueous solution of the diacid with one equivalent of a standardized potassium hydroxide solution and 15 subsequent lyophilization. The phosphodiester diacid (579 mg, 0.927 mmole) was dissolved in 57.9 ml of water and treated with 9.44 ml of 0.0986 N potassium hydroxide solution (0.931 mmole). The neutralized solution was then lyophilized to remove water and yield 603 mg (98%) of mono potassium salt as a fluffy white solid.

20

EXAMPLE 2

Purification by Reverse Phase C-18 Chromatography

Reverse Phase C-18 silica gel was prepared on a 1 kg scale according to Evans, *Chromatographia*, Vol. 13, pages 5-10 (1980). 25 Purification of the phosphodiester acid to a level of 90% was achieved at a 90:1 load ratio using 1:1 THF/water, followed by THF removal in a stream of nitrogen and water removal by lyophilization. Investigation of

other solvent systems by reverse phase thin layer chromatography has good potential to (i) improve the level of purity, (ii) identify an effective separation medium that could be removed by rotary evaporation, and (iii) allow the use of a lower load ratio. Since the reverse phase C-18 5 silica gel is reusable, the method has good potential for purification up to 1000 grams.

Solvent systems that are suitable include THF/methanol, THF/ethanol, THF/isopropanol, dioxane/methanol, dioxane/ethanol, dioxane/isopropanol, ether/methanol, ether/ethanol, ether/isopropanol, 10 ethyl acetate/methanol, ethyl acetate/ethanol, ethyl acetate/isopropanol, methylene chloride/ethanol, methylene chloride/methanol, methylene chloride/isopropanol, DME/methanol, DME/ethanol and DME/isopropanol.

Conjugation with cholesterol converts the polar ascorbic acid to 15 a more non-polar lipophilic ascorbyl group that is readily absorbed through the stratum corneum. Once past the stratum corneum, the absorbed compound is able to effect underlying fibroblasts. The benefits of bioreversed ascorbic acid and cholesterol have been previously explained. Surprisingly, the conjugated compound itself 20 stimulates collagen synthesis which enhances the integrity, elasticity and resiliency of skin. Additional details are provided in Example 3.

EXAMPLE 3

Fibroblast Studies

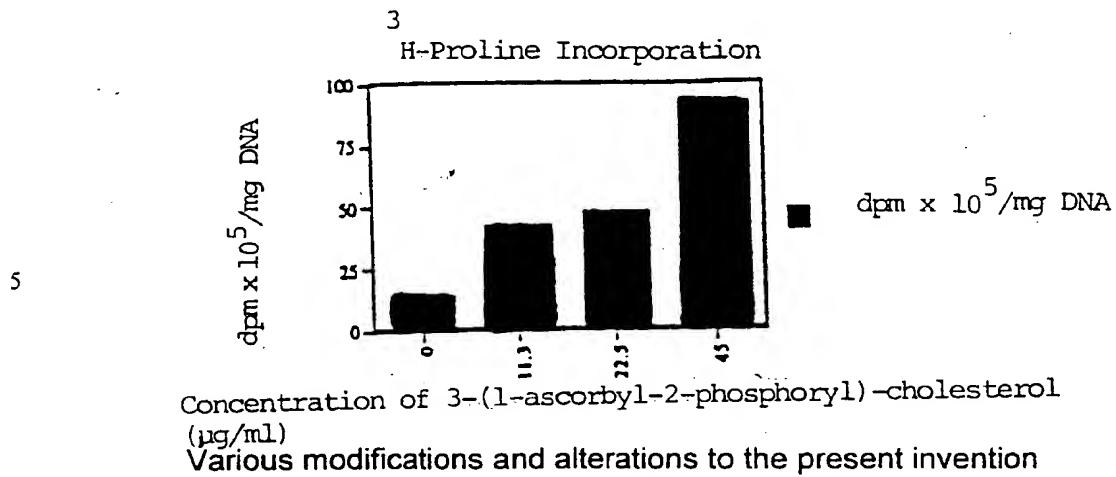
25 This example summarizes a study in which the ability of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol to stimulate collagen production in cultured human skin fibroblasts is demonstrated. An art-recognized

[³H]-Proline Incorporation Assay was performed with different doses of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol. Juva, Anal. Biochem., Vol. 15, pages 77-83 (1966); Booth, Biochem. Biophys. Acta, Vol. 675, pages 117-122 (1981).

5 Fibroblasts were incubated with 0 µg/ml, 11.3 µg/ml, 22.5 µg/ml and 45 µg/ml of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol for a total of 48 hours. After the first 24 hours [³H]-labeled proline was added to the culture. Following the second 24 hour period, the cells are harvested and prepared for the collagen biosynthesis assay.

10 Protease inhibitors are added to prevent degradation of collagen and other proteins. The cell layer is scraped into a solution containing 0.4 M NaCl and 0.01 M Tris (pH 7.5). Extracts are sonicated to disrupt cell membranes. Separate volumes of the cell-containing solution (1 ml each) are dialyzed overnight against several changes of deionized 15 water. The retentate is removed from dialysis and hydrolyzed in 6 N hydrochloric acid at 120 degrees C overnight. The assay is performed using an oxidation process with 2 M chloramine-T. Samples are analyzed for radioactive counts, which represent the amount of newly synthesized [³H]-hydroxyproline -- an index for new collagen synthesis.

20 It was discovered that 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol increased production of new collagen by human skin fibroblasts in a dose dependent manner as illustrated by the following chart.



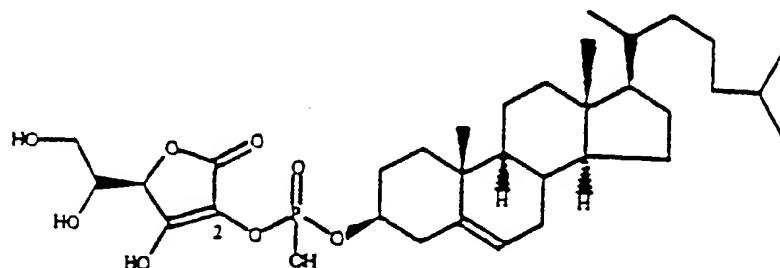
may be appreciated based on a review of this disclosure. These
10 changes and additions are intended to be within the scope and spirit of
this invention as defined by the following claims.

WHAT IS CLAIMED IS:

1. A topical formula comprising a suitable topical vehicle
and a compound having the formula

5

10



2. A topical formula comprising a suitable topical vehicle
15 and a compound selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol or homologs and salts thereof.

20 3. The topical formula of claim 2, wherein said salt is
selected from the group consisting of ammonium, calcium, lithium,
potassium, sodium and an organic amine.

4. The topical formula of claim 2, wherein said compound is
selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-
cholesterol and 3'-(L-ascorbyl-3-o-phosphoryl)-cholesterol.

25

5. The topical formula of claim 2, wherein said vehicle is
selected from the group consisting of a lotion, cream and gel.

6. The topical formula of claim 2, wherein said compound is about .0001 to about 100 weight percent.

7. The topical formula of claim 2, wherein said compound is
5 about .05 to about 50 weight percent.

8. The topical formula of claim 2, wherein said compound is about .10 to about 20 weight percent.

10 9. The topical formula of claim 2, wherein said compound is about 1.0 to about 10 weight percent.

10. The topical formula of claim 5, wherein the pH of the
topical formula is adjusted to physiologically acceptable levels with
15 sufficient amounts of a compound selected from the group consisting of
ammonium hydroxide, calcium hydroxide, lithium hydroxide, potassium
hydroxide, sodium hydroxide, ethanolamine, diethanolamine and urea.

11. A lotion comprising about 0.10 to about 20.0 weight percent
20 of a compound selected from the group consisting of 3'-(L-ascorbyl-2-o-
phosphoryl)-cholesterol or homologs and salts thereof, and the
remainder including water.

12. The lotion of claim 11, further comprising from about .001
25 to about 1.5 weight percent thickening agent.

13. The lotion of claim 12, wherein said thickening agent is selected from the group consisting of xanthene gum, hydroxyethyl cellulose or a combination thereof.

5 14. A topical formula comprising:

(a) about 0.10 to about 20.0 weight percent of a compound selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol or homologs and salts thereof;

10

(b) about 0.5 to about 6.0 weight percent emollient;

15

(c) about 4.8 to about 14.5 weight percent emulsifier; and,

(d) about 0.5 to about 1.4 weight percent thickening agent.

15. The topical formula of claim 14, further comprising about 0.35 to about 0.45 weight percent preservative.

20

16. The topical formula of claim 15, wherein the emollient is glycerin; and wherein the emulsifier is a combination of about 2.0 to about 8.0 weight percent of propylene glycol decapitate, about 1.8 to about 4.0 weight percent of Peg 40 Stearate, and about 1.0 to about 2.5 weight percent of Steareth-2.

25

17. The topical formula of claim 16, wherein the thickening agent is about 0.25 to about 0.70 weight percent of xanthene gum and about 0.25 to about 0.70 weight percent of hydroxyethyl cellulose.

5 18. The topical formula of claim 17, wherein the preservative is about 0.15 to about 0.20 weight percent of an EDTA salt, and about 0.20 to about 0.25 weight percent of methylparaben.

10 19. A cream comprising:

about 0.10 to about 20.0 weight percent of a compound selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol or homologs and salts thereof;

15 about 0.1 to about 1.2 weight percent of a thickening agent;

about 0.1 to about 15 weight percent of an emulsifier; and,

the remainder including water.

20 20. The cream of claim 19, further comprising up to about 1 weight percent of fragrance.

25 21. A cream comprising:

(a) about 0.1 to about 20.0 weight percent of a compound is selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol or homologs and salts thereof;

5 (b) about 0.5 to about 4.0 weight percent emollient;

(c) about 2.0 to about 6.0 weight percent emollient/humectant;

10 (d) about 4.5 to about 11.0 weight percent emulsifier;

(e) about 0.5 to about 1.2 weight percent thickening agent; and,

15 (f) about 0.15 to about 0.2 weight percent preservative.

22. The cream of claim 21, wherein the emollient is glycerin; and wherein the emollient/humectant is propylene glycol decapitate; and wherein the emulsifier is about 1.8 to about 3.0 weight percent Steareth-20, about 0.8 to about 2.0 weight percent Steareth-2, about 1.0 to about 2.5 weight percent cetyl alcohol, and about 0.9 to about 3.5 weight percent glycerol mono-stearate; and wherein the thickening agent is about 0.25 to about 0.6 weight percent xanthene gum and about 0.25 to about 0.6 weight percent hydroxyethyl cellulose.

25

23. The cream of claim 22, wherein the preservative is an EDTA salt.

24. A gel comprising:

about 0.10 to about 20 weight percent of a compound is
5 selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-
cholesterol or homologs and salts thereof;

about 0.30 to about 2.0 weight percent thickening agent; and,
10 the remainder including water.

25. A gel comprising:

about 0.10 to about 20.0 weight percent of a compound is
15 selected from the group consisting of 3'-(L-ascorbyl-2-o-phosphoryl)-
cholesterol or homologs and salts thereof;

about 2.0 to about 6.0 weight percent emollient/humectant;
20 about 0.4 to about 1.5 weight percent thickening agent; and,

about 0.35 to about 0.45 weight percent preservative.

26. The gel of claim 25, wherein the emollient/humectant is
25 propylene glycol; wherein the preservative is about 0.20 to about 0.25
weight percent methylparaben, and about 0.15 to about 0.20 weight
percent an EDTA salt; and wherein the thickening agent is selected from

